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# EFFECTS OF TAMOXIFEN ON PERIODONTAL STATUS

# ЕФЕКТОТ НА ТАМОКСИФЕН ВРЗ ПАРОДОНТАЛНИОТ СТАТУС

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## Abstract

Tamoxifen is a selective estrogen receptor modulator (SERM) or a partial estrogen receptor (ER) agonist. It has mixed estrogenic and antiestrogenic activity, with a profile of effects that differ by tissue. For example, tamoxifen has predominantly antiestrogenic effects in the breast, but predominantly estrogenic effects in other tissues where it has an estrogen receptor. In breast tissue, tamoxifen acts as an ER antagonist by inhibiting the transcription of estrogen-responsive genes. **Aim:** The purpose of this study was to follow the effects of tamoxifen therapy on periodontal disease on oncological patients (Carcinoma Mammae). **Material and method:** In order to achieve the goal of the study, 75 examinees were included. All examinees were divided into four groups. The subjects who were involved in the research signed a written consent, which enabled us to use the obtained data for scientific and research purposes. The first three groups were subjects with Ca Mammae who completed the appropriate therapy and started receiving tamoxifen. The fourth group (control) were healthy subjects who did not receive tamoxifen. **Results:** For 75 subjects included in the examination, the index of gingival inflammation varies in the interval 0.87 ± 0.99; ± 95.00% CI: 0.64-1.09; the minimum value is 0.00 and the maximum 3.00. **Conclusion:** Our research has shown that in patients with breast cancer treatment with tamoxifen for more than two years leads to reduction of inflammatory processes in the periodontium. **Key words:** gingival inflammation, tamoxifen, breast cancer, oral health, chemotherapy.

## Апстракт

Тамоксифен делува како селективен модулатор на естрогенски рецептори (SERM) или како делумен агонист на естрогенските рецептори (ЕР). Има мешана естрогена и антиестрогена активност, со профил на ефекти кои се разликуваат по ткиво. На пример, тамоксифен има претежно антиестрогени ефекти во градите, но претежно естрогени ефекти во другите ткива каде што има естрогенски рецептор. Во ткивото на градите, тамоксифен делува како антагонист на ЕР така што е инхибирана транскрипцијата на гените кои одговараат на естрогенот. **Цел на трудот:** Целта на овој труд беше преку клинички испитувања да се проследат ефектите од терапијата со тамоксифен врз пародонтот кај онколошките пациенти (Ca Mammae). **Материјал и метод:** За реализација на поставената цел во истражувањето беа вклучени 75 испитаници поделени во четири групи. Испитаниците кои беа вклучени во истражувањето потпишаа писмена согласност, со што ни беше овозможено добиените податоци да ги искористиме во научно-истражувачки цели. Првите три групи беа испитаници со Ca Mammae кои ја завршиле соодветната терапија и започнале со примање на тамоксифен. Четвртата група (контролна) ја сочинуваа здрави испитаници кои не примаат тамоксифен. **Резултати:** Кај 75 испитаници вклучени во испитувањето индексот на гингивална инфламација варира во интервалот 0,87±0,99; ±95,00%CI:0,64-1,09; минималната вредност изнесува 0,00 а максималната 3,00. **Заклучок:** Нашето истражување покажа дека кај пациентите со рак на дојка третирани со терапија со тамоксифен повеќе од две години доведува до намалување на воспалителните процеси на пародонтот. **Клучни зборови:** гингивална инфламација, тамоксифен, рак на дојка, орално здравје, хемотерапија.

## Introduction

Tamoxifen (TAM) has been the drug of choice in breast cancer treatment for more than 20 years. In fact, this synthetic non-steroidal compound inhibits the binding of natural estrogen to its receptors, therefore inhibiting the proliferation of tumor cells dependent on it. Its effect is specific and has no affinity for the progesterone receptor or other steroids; it has antitumor and cytostatic use[1], it is also used as a therapy for other cancers[2]. Tamoxifen is usually taken orally (per os) every day for five years for breast cancer[3]. It is a selective estrogen receptor modulator (SERM) and reduces the growth of breast cancer cells[3,4]. It is a member of the group of triphenylethylene compounds[5].

Tamoxifen is currently used to treat early and advanced estrogen receptor-positive (ER-positive or ER +) breast cancer in pre- and postmenopausal women[6].

A beneficial effect of tamoxifen is that it prevents bone loss by acting as an estrogen receptor agonist (i.e., mimicking the effects of estrogen) in this type of cell. Therefore, by inhibiting osteoclasts, it prevents osteoporo-

sis[7,8]. Estrogen receptors are located in all layers of the gingival epithelium, buccal mucosa, and salivary glands, it's the effect of tamoxifen on oral health. Estrogen receptors exist as two subtypes, the estrogen receptor alpha (EPα) and the estrogen receptor beta (EPβ)[9]. Some research articles have shown that ERa was completely undetected in oral tissues, whereas ERb was expressed in high levels in oral epithelium and salivary glands[10, 11]. The differential expression of ERb in these tissues may account for the conflicting results in estrogen receptor expression in earlier studies. In this study, the results show that a tissue-specific subtype distribution is also observed in oral tissues with ERb but not ERa. ERa is usually expressed in classic target tissues, such as breast tissue. The identification of ERb in these tissues has significant clinical importance and suggests a direct role for estrogen in the physiology of the oral mucosa and salivary gland function[10].

Tamoxifen is a selective estrogen receptor modulator (SERM) or a partial estrogen receptor (ER) agonist. It has mixed estrogenic and antiestrogenic activity, with a profile of effects that differ by tissue. For example, tamoxifen has predominantly antiestrogenic effects in the breast, but predominantly estrogenic effects in other tissues where it has an estrogen receptor. In breast tissue, tamoxifen acts as an ER antagonist by inhibiting the transcription of estrogen-responsive genes[12].

## Aim of the study

The aim of this study was to follow the effects of tamoxifen therapy on periodontal status of oncological patients with Carcinoma Mammae.

## Material and method

In order to achieve the goal in the survey, 75 examinees were included. All examinees were divided into four groups. The subjects who were involved in the research signed a written consent, which enabled us to use the obtained data for scientific and research purposes. The first three groups were subjects with Carcinoma Mammae who completed the appropriate therapy and started receiving tamoxifen. The fourth group (control) were healthy subjects who did not receive tamoxifen.

- Group 1 - 15 patients with diagnosed breast cancer, treated with TAM for 1 month to 2 years.
- Group 2 - 15 patients with diagnosed breast cancer, treated with TAM for 2-5 years.
- Group 3 - 15 patients with diagnosed breast cancer, who have finished their treatment with TAM (after 5 years).
- Group 4 (control) - 30 healthy patients who did not receive TAM.

All data obtained from clinical trials were noted in a card prepared for that purpose for each patient separately. The card contained generalities of the examinee, anamnestic data about the disease, this part of the card was filled only for the examinees from the first three groups. For determining the condition of the gingiva, we used the index (Silness&Loe) according to the following index values: 0 = absence of inflammation - normal gingiva, 1= slight inflammation, slight discoloration, slight edema, no bleeding during probing, 2 = moderate inflammation moderate redness, swelling, bleeding when probing, hypertrophy and 3 = severe inflammation redness and hypertrophy, ulceration, tendency to spontaneous bleeding.

### STATISTICAL ANALYSIS

The data analysis was performed in a statistical program STATISTICA 8.0 and SPSS Statistics 23.0

## Results

Descriptive statistics on gingival inflammation (Silness&Loe index) is shown in Table 1.

In the four groups the gingival inflammation index varies in the range 0.87±0.99; ±95.00% CI: 0.64-1.09; the minimum value is 0.00 and the maximum value is 3.00.

In the control group, healthy patients who did not receive TAM, the value of gingival inflammation in the Silness &Loe index varies in the interval 1,100±0.99. In the first group, patients treated with tamoxifen for 1

**Table 1.** Gingival inflammation (Silness &Loe index)

| Variable | Valid N | Mean | Confidence -95,00% | Confidence +95,00 | Minimum | Maximum | Std. Dev. |
|---|---|---|---|---|---|---|---|
| Gingival inflammation Silness&Loe index | 75 | 0.87 | 0.64 | 1.09 | 0.00 | 3.00 | 0.99 |

month to 2 years, the value of gingival inflammation in the Silness &Loe index varies in the interval 1.067±1.01. In the second group, patients treated with tamoxifen for 2 to 5 years, the value of gingival inflammation in the Silness &Loe index varies in the interval 0.667±0.98. In the third group, patients who have finished their treatment with tamoxifen after 5 years, the value of gingival inflammation in the Silness &Loe index varies in the interval 0.400±0.83. (Table 1.1).

For Kruskal-Wallis ANOVA by Ranks=6,44 и p>0,05(p=0,09) values of gingival inflammation between the examinees from the four groups, no statistically significant difference was found. (Table 1.2)

The results shown in Figure 1. refer to the investigated relationship between the treatment with tamoxifen and the index of gingival inflammation following Silness&Loe. For Spearman Rank Order R=-0.27 (p<0.05) a moderately strong negative significant correlation was found. With the increase of treatment with tamoxifen over time, the index of gingival inflammation significantly decreases.

The results shown in Table 1.3 refer to the multiple regression refer to the investigated relationship between

**Table 1.1** Breakdown Table of Descriptive Statistics / Gingival inflammation (Silness &Loe index)

| Tamoxifen | Gingival inflammation Means | Gingival inflammation N | Gingival inflammation Std.Dev. |
|---|---|---|---|
| Healthy patients who did not receive TAM | 1,100 | 30 | 0.99 |
| Treated with TAM for 1 month to 2 years | 1,067 | 15 | 1.03 |
| Treated with TAM for 2-5 years | 0,667 | 15 | 0.98 |
| Finished their treatment with TAM (after 5 years) | 0,400 | 15 | 0.83 |
| All Grps | 0,867 | 75 | 0.99 |

**Table 1.2.** Gingival inflammation (Silness &Loe index)/ Kruskal-Wallis ANOVA by Ranks

| Gingival inflammation (Silness&Loe) | Code | Valid N | Sum of Ranks |
|---|---|---|---|
| Healthy patients who did not receive TAM | 0 | 30 | 1276,50 |
| Treated with TAM for 1 month to 2 years | 1 | 15 | 631,50 |
| Treated with TAM for 2-5 years | 2 | 15 | 510,00 |
| Finished their treatment with TAM (after 5 years) | 3 | 15 | 432,00 |

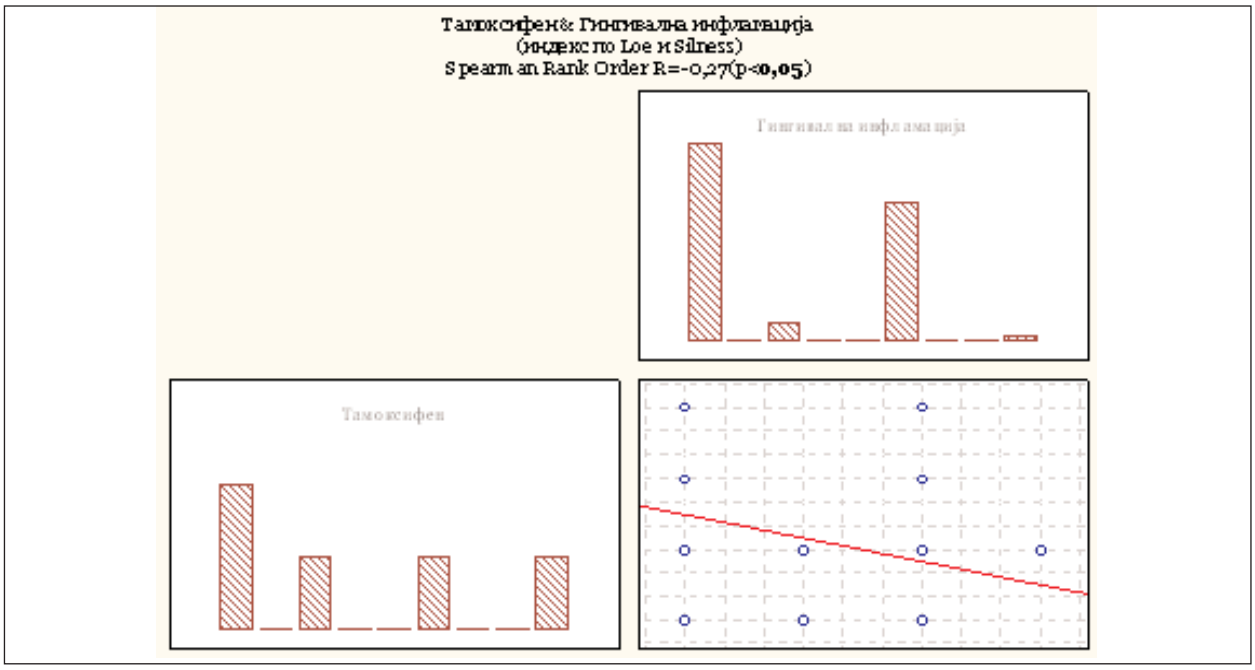


**Figure 1**

**Table 1.3.** Gingival inflammation (Silness &Loe index) / Treatment with tamoxifen

| **Regression Summary for Dependent Variable: Gingival inflammation ( Sillnes&Loe index); R= 0,29; F=2,17 and p=0,099** | | | | | | |
|---|---|---|---|---|---|---|
| N=75 | Beta | Std.Err. of Beta | B | Std.Err. of B | t(71) | p-level |
| Intercept | | | 1,10 | 0,18 | 6,22 | 0,000 |
| Treated with TAM for 1 month to 2 years | -0,01 | 0,12 | -0,03 | 0,31 | -0,11 | 0,91 |
| Treated with TAM for 2-5 years | -0,18 | 0,12 | -0,43 | 0,31 | -1,42 | 0,16 |
| Finished their treatment with TAM (after 5 years) | -0,28 | 0,12 | -0,70 | 0,31 | -2,29 | **0,03** |

the index of gingival inflammation following Silness&Loe as a dependent variable and during time of treatment with tamoxifen.

Healthy patients who did not receive tamoxifen were taken as a reference category (control group).

For R=0.29 (F=2.17 and p=0.099) a moderately strong correlation was determined.

The greatest impact on gingival inflammation has treatment with tamoxifen for more than 5 years (Beta=-0.28 (p<0.05), followed by treatment with tamoxifen for 2 to 5 years (Beta=-0.18 (p>0.05)), while the weakest effect of tamoxifen treatment is from 1 month to 2 years (Beta =-0.01 (p>0.05).

Examinees treated with tamoxifen for more than 5 years had an average of -0.70 (p <0.05/p=0.03) significantly lower values of gingival inflammation compared to healthy subjects who did not receive tamoxifen.

Examinees treated with tamoxifen for 2 to 5 years had an average of -0.43 (p> 0.05 / p=0.16) slightly lower val-

ues of gingival inflammation compared to healthy subjects who did not receive tamoxifen.

Examinees treated with tamoxifen from 1 month to 2 years had an average of -0.03 ($p>0.05$ / $p=0.91$) slightly lower values of gingival inflammation compared to healthy subjects who did not receive tamoxifen.

## Discussion

If the gingival inflammation (gingivitis) is treated, the condition is reversible without lasting consequences. On the other hand, untreated cases can lead to more complex and destructive changes that result in chronic periodontal disease, with ultimate consequences – premature decomposition and loss of teeth.

Estrogen plays a regulatory role in maintaining the balance between osteoblast production and osteoclast production. Several studies suggest that osteoporosis is a risk factor for periodontal disease and loss of teeth[13,14,15,16,17]

The results obtained from the clinical examination included the determination of the index values for determining the condition of the gingival inflammation among our examinees which varied in the interval 0.87 ± 0.99; ± 95.00% CI: 0.64-1.09; the minimum value is 0.00 and the maximum value is 3.00. (shown in Table 1.) Table 1.2 shows the values of gingival inflammation between the examinees from the four groups and no statistically significant difference was found.

The results acquired for the relationship between duration of the treatment with tamoxifen and gingival inflammation shown in Figure 1 show moderately strong negative significant difference $R=-0.27$ ($p<0.05$). Patients with diagnosed breast cancer, who have been treated with tamoxifen for many years, have a reduction in inflammatory changes in the periodontium, and improvement in periodontal health. Our results are consistent with the results of Milagros et al., a long time of tamoxifen consumption there has a growing trend towards gingival health[18].

## Conclusion

Chronic treatment with tamoxifen has a tendency to revert periodontal disease in patients suffering from breast cancer. At longer time of tamoxifen consumption has a growing trend towards gingival health.

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